UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,283	02/02/2004	Michael P. Maher	AUROBIO.026D2D1	9653

20595 7590 11/13/2009

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
FERNANDEZ, SUSAN EMILY	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
11/13/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/771,283	MAHER ET AL.	
	Examiner	Art Unit	
	SUSAN E. FERNANDEZ	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 10, 2009, has been entered.

Claims 1-7 are pending and examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Catterall et al. (US 5,437,982) in view of Connolly et al. (Biosensors and Bioelectronics. 1990. 5: 223-234) and Kovacs et al. (US 5,981,268).

Catterall et al. discloses a method of identifying specific inactivation gate inhibitors of a sodium channel. Example 1 describes the steps involved in this method, wherein the host cells, Chinese hamster ovary cells, are first transfected with wild-type Type IIA sodium channels, the target ion channels (column 13, lines 10-13). Additionally, mutant (F1489Q) sodium channels are also expressed in other host cells (human kidney carcinoma cells), and these mutant channels are also target ion channels. The effects of a drug candidate, the KIFMK gate peptide, is observed on these target ion channels by introducing the KIFMK gate peptide into the cells (column 13, lines 18-27), and then applying a series of 10 Hz voltage pulses which were applied at different voltages (column 13, lines 27-29). These voltage pulses are depolarizing and activate (open) the Type IIA sodium channels (column 5, lines 42-44). Therefore, limitations in instant claims 5 and 6 are taught by the reference. It is noted that the ion channel is cycled between different voltage dependent states (closed state to an open state, or closed state to an inactivated state), as the cell membrane of the Chinese hamster ovary cells are repetitively depolarized (column 6, lines 1-7). Thus, the transmembrane potential is set to a level suitable for a specific ion channel activation state or transition between states, as required by instant claim 1. With respect to the inhibitory effect of KIFMK on sodium channels, the experiments demonstrated that, "...there is no appreciable block when the channels are not repetitively cycling between the closed, activated and inactivated states" (column 13, lines 59-62). Clearly, limitations of instant claim 4 are taught by Catterall et al. Since the magnitude of the sodium currents in the

experimental and control preparations were compared (column 13, lines 31-33), detection of transmembrane potential characteristics on the cells over and area of observation was performed to detect an effect of the candidate drug compound on the target ion channel, as required by instant claim 1.

Catterall et al. differs from the claims under examination in that Catterall et al. does not expressly disclose that the repetitive application of electric fields taught in the reference is applied with extracellular electrodes. Instead, Catterall et al. discloses using filled electrodes which break through the cell membrane.

Connolly et al. teaches that when saline-filled glass microelectrodes for monitoring cell electrical activity which are positioned inside the cell membrane, are used "...there is always some risk of rupturing the cell membrane and destroying the cell," and that "it is difficult and very time consuming to work with several glass microelectrodes simultaneously *in vivo* or *in vitro*..." (page 223, last paragraph through page 224, first paragraph). As an alternative, Connolly et al. teaches extracellular electrodes (page 224, second paragraph). Though these extracellular electrodes are taught for monitoring cell electrical activity, it is noted that "it was found that extracellular stimulation of the cells was possible via the same electrodes used for recording" (page 223, abstract, last sentence).

Kovacs et al. teaches "...an apparatus and method for monitoring cells, which apparatus and method are capable of activating a voltage-gated ion channel, while detecting the impedance of individual cells, and changes therein" (column 4, lines 3-7). Also taught is "...an apparatus and method for monitoring cells, which apparatus and method are capable of detecting and/or measuring the action of a pharmaceutical agent, drug...by monitoring the impedance and/or

action potential parameters of individuals cells, and changes therein" (column 4, lines 15-21). The apparatus comprises planar microelectrodes disposed on a substrate (column 7, lines 8-10) where the cells are cultured within a medium in a layer adhered to the surfaces of the microelectrode array (column 7, lines 27-29). Therefore, the method for detecting and/or measuring the action of a pharmaceutical agent (thus drug candidate) uses extracellular electrodes. For example, in a study of a sodium channel blocker tetrodotoxin (TTX) (column 18, lines 18-67) an electrical signal between each microelectrode and a reference electrode is selectively applied (column 18, lines 55-57).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have practiced the Catterall invention as discussed above with extracellular electrodes. One of ordinary skill in the art would have been motivated to do this since electrodes inserted into cells have the disadvantages of possibly destroying the cells, and may be difficult and time consuming to use. Also, pointed out in Connolly et al., extracellular electrodes would have served as suitable substitutes of electrodes which are positioned inside cells. The appropriateness of applying voltage pulses to the cells by extracellular electrodes rather than by the method as taught in Catterall is demonstrated in Kovacs et al., which also shows that extracellular electrodes are suitable for applying electrical signal to cells to activate a voltage-gated ion channel.

Additionally, it would have been obvious to have performed various assays for identifying specific inactivation gate inhibitors of a sodium channel simultaneously by performing the method in various containers (wells) simultaneously.

Catterall et al. also differs from the claimed invention in that Catterall et al. does not expressly disclose that the frequency of the electric field pulses are within the range of $\tau_M^{-1} \leq f \leq \tau_b^{-1}$ where τ_M is a time constant for decay of transmembrane potential changes, and τ_b is an average target ion channel open time, or that the pulses at said frequency cause a sustained transmembrane potential via a stepwise accumulation or loss of ions. However, the selection of a specific suitable electric field pulse frequency range, including that claimed, clearly would have been an obvious matter of optimization on the part of the artisan of ordinary skill, particularly in view of the disclosure in Catterall et al. that the inhibitory effect of a drug candidate (KIFMK) on the sodium channel is frequency-dependent (column 13, lines 56-62). Moreover, Catterall et al. teaches that a depolarization voltage can be adjusted in a stepwise manner (column 14, lines 4-8). Thus, there would have been a stepwise accumulation or loss of ions. It would have been obvious to adjust the depolarization voltage in a stepwise manner in the drug screening example of Catterall et al. (Example 1) since it would have given the predictable result of depolarizing (hence activating) the cells for the purposes of drug screening.

Thus, a holding of obviousness is clearly required.

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Catterall et al., Connolly et al., and Kovacs et al. as applied to claims 1, 2, and 4-6 above, and further in view of Tung et al. (Biophysical Journal, 1992, 63(2): 371-386).

As discussed above, Catterall et al., Connolly et al., and Kovacs et al. render claims 1, 2, and 4-6 obvious. However, these references do not expressly disclose repetitive application of biphasic electric fields.

Tung et al. discloses comparison of the effects of biphasic and monophasic electric fields on the electrical stimulation of cardiac cells (abstract). It was noted that "strength-duration curves derived from field stimulation show that over a wide range of pulse durations, biphasic waveforms can recruit and activate membrane patches about as effectively as can monophasic waveforms having the same total pulse duration" (abstract).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to practice the screening method with biphasic electric fields instead of monophasic electric fields.

One of ordinary skill in the art would have been motivated to make this substitution in order to have stimulated the cells with a reasonable expectation of success.

Thus, a holding of obviousness is clearly required.

Claims 1, 2, and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Catterall et al., Connolly et al., and Kovacs et al. as applied to claims 1, 2, and 4-6 above, and further in view of Tsien et al. (WO 96/41166) or Denyer et al. (Drug Discovery Today, 1998, 3(7): 323-332).

As discussed above, Catterall et al., Connolly et al., and Kovacs et al. render claims 1, 2, and 4-6 obvious. However, these references do not expressly disclose a method wherein the host cells comprise a voltage sensor.

Tsien et al. discloses a screening method for identifying drugs that affect ion channel activity corresponding to changes in membrane potentials in cells (pages 42 and 43). The invention comprises the steps of loading the cells with first and second reagents for measuring

membrane potential (page 42, lines 31-33). The first reagent comprises a transmembrane potential redistribution dye, also described as a hydrophobic fluorescent ion capable of redistribution upon changes in membrane potential (page 3, lines 7-11). Furthermore, the transmembrane potential redistribution dye is considered an ion sensitive fluorescent molecule and an electrochromic transmembrane potential dye. The second reagent comprises a chromophore, preferably a fluorophore capable of FRET or electron transfer (page 3, lines 25-30). Thus the second reagent is considered a FRET based voltage sensor, an electrochromic transmembrane potential dye, or an ion sensitive fluorescent molecule.

Denyer et al. reviews high throughput screening (HTS) methods for voltage-gated ion channel modulators. Radiotracers, including radioactive ions, are noted for their use in tracing ion flux through ion channels (page 328). Furthermore, high throughput methods have been established for enabling ion channel assays with radiotracers.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to have injected the host cells of the Catterall invention with the voltage sensors disclosed in Tsien et al. or the radiotracers disclosed in Denyer et al.

One of ordinary skill in the art would have been motivated to do this since the use of voltage sensors disclosed in Tsien et al. and Denyer et al. would served equivalently to the current measurements taught in Catterall et al. in measuring the effect of the drug candidate on the target ion channels.

A holding of obviousness is clearly required.

Response to Arguments

Applicant's arguments filed June 10, 2009, have been fully considered but they are not persuasive. The applicant asserts that the post-filing date art (Nature Biotech. 24(4). April 2006; Augustine) shows that the person of ordinary skill in the art at the time the invention was made would not find it obvious to manipulate transmembrane potential as claimed with extracellular electrodes. While MPEP 2164.05(a) indicates that "…if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application," Kovacs et al. provides evidence contrary to the teachings of the post-filing date art pointed out by the applicant. Kovacs et al. demonstrates that the use of extracellular electrodes to apply energy to cells and to activate a voltage-gated ion channel was known at the time the invention was made. Therefore, the claims must be rejected over Catterall et al., Connolly et al., and Kovacs et al.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN E. FERNANDEZ whose telephone number is (571)272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Susan E. Fernandez
Examiner
Art Unit 1651

sef